REMARKS

With the entry of the present Amendment, claims 51-63, 66-89 and 91-94 are in this application. Claim 90 has been cancelled and replaced with new claim 94 in order to more easily adjust punctuation and for better clarity. Claims 91-93 have been amended to update dependency. Claims 62 and 66-69 have been amended to better claim the invention. Claim 69 has been amended to recite a particular ratio of cell number; support is found in as-filed Specification at page 7, lines 23-24, for example. None of the amendments made herein constitutes the addition of new matter.

The Rejections under 35 U.S.C. 112, second paragraph

Claims 62, 63, 66-75 and 93 have been rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite.

Claim 62 is said to recite the new limitation directed to non-hepatocyte cell type maintain its cell phenotype and that it is not clear what phenotype of the non-hepatocyte cell type is being maintained.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended claim 62 to clarify that the secretory phenotype that is maintained. Support is found in the as-filed Specification at page 25, lines 1-5.

Claim 69 is said to disclose a ratio of cells of between 0.5:2 and 2:0.5 gall bladder epithelial cells:hepatocytes. It is noted that the limitation was amended to disclose cells of. The Patent Office is alleging it is still not clear whether or what parameter this ratio is based on – number, volume, etc of cells. Clarification is required.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended claim 69 to recite there is a ratio of hepatocyte cell number to non-hepatocyte cell number of 1:1. Applicants respectfully submit that the claim as

amended meets the requirements of the statute for clarity and is consistent with the original claim, which would have been understood by the skilled artisan to mean a ratio of cell numbers. Accordingly, the withdrawal of the rejection is respectfully requested.

Claims 90-03 are allegedly unclear in the use of or and "and" as well as in the recitation of "type".

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have cancelled claim 90 without prejudice and new claim to delete "or" in line 5, to replace "and/or" in line 7 with "or" and by inserting semicolons between groups for improved clarity. In addition, "type" has been deleted. Accordingly, the withdrawal of the rejection is respectfully requested.

Claim 91 is allegedly indefinite in the recitation of "the hepatocytes", as lacking antecedent basis.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended claim 90 to recite hepatocytes; thus antecedent basis is provided, and the withdrawal of the rejection is respectfully requested.

<u>The Rejections under 35 U.S.C. 112, first paragraph</u>

Claims 90-93 have been rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement and allegedly containing new matter. Applicants respectfully traverse this rejection.

The previous amendment to claim 90 to insert "differentiated" was deemed to contain new matter.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended claim 62 to delete the recitation of "differentiated" and replace

it with "wherein said cell maintains its secretory phenotype". Support is found at page 23, lines 19-20 and 22-25, page 24, lines 5-6, page 25, lines 3-5, and at Example 2 of the as-filed Specification.

In view of the amendments to the claims and discussion above, Applicants respectfully request the withdrawal of this rejection.

The Rejections under 35 U.S.C. 102/103

Claims 62, 66-68 and 70-74 have been rejected under 35 U.S.C. 102(b) or 103(a) as allegedly unpatentable over Kobayashi (1991) Gastroenterologica Japonica or Lee et al. (2003) Am. J. Physiol. Gastrointest. Liver Physiol. Applicants respectfully traverse this rejection.

The cited references are each said to teach a culture of human gall bladder epithelial cells. The Patent Office has indicated that the stated intended use of the claimed compositions (for implantation) has no weight. The Patent Office has further stated that "the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's function, does not render the old composition patentably new to the discoverer".

Applicants respectfully maintain the Kobayashi describes a cell culture protocol but not an implantable composition of gall bladder epithelial cells (GBEC). As reported at page 367, first paragraph, the GBEC were cultured for 5 days until growth was confluent, and the cells were then detached from the culture plates but could not be subcultured further and only survived an additional 7 days in the new culture dish. Such cells are not suitable for implantation, and this is certainly appreciated by one of ordinary skill in the relevant art. Moreover, the Kobayashi reference indicates that the GBEC were derived from material removed from patients with bladder stones. Nowhere does the cited Kobayashi reference state that the patients were neonates.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended claim 62 to recite a particular ratio of hepatocyte cell number to non-hepatocyte cell number. This limitation has been imported from as-filed claim 69, and claim 69 is now amended to recite a particular ratio. Applicants note that claim 69 had not been included in either the Section 102 or the Section 103 rejection; thus, Applicants believe that claim 62 as amended should now be allowable. The ratios recited are neither disclosed nor suggested in the cited references. Table 2.3 of the present application shows an imparted rate of Factor VIII secretion by non-hepatocyte cells when they are co-cultured with hepatocytes. This result taught by present Applicants was not part of the prior art, nor could it have been predicted with any reasonable expectation of success.

Moreover. the cited Lee reference describes secretion of apoA-I and apoA-E from cultured canine GBECs. Nowhere does the cited Lee reference state that the cultured cells were neonatal GBECs.

In view of the foregoing, Applicants respectfully submit that the present claimed invention is not anticipated by either the cited Kobayashi reference or the cited Lee reference, nor is the invention as presently claimed *prima facie* obvious over the cited references. Accordingly, the withdrawal of the rejection is requested.

Claims 62-63, 66-68, 70-75 and 89 have been rejected under 35 U.S.C. 102(b) or 103(a) as allegedly unpatentable over Clement et al. (1984) Hepatology. Applicants respectfully traverse this rejection.

The Patent Office has interpreted the present claimed compositions as comprising hepatocytes and gall bladder epithelial cells. Clement is said to teach a co-culture system comprising hepatocytes and gall bladder epithelial cells. Again, the Patent Office indicated that the stated intended use of the claimed compositions (for implantation) has no weight.

The cited Clement reference describes a co-culture system of human hepatocytes with rat liver epithelial cells (RLECs), wherein the RLECs enhance deposition of extracellular material (EM) around the hepatocytes. EM deposition enables the hepatocytes to survive in culture for longer periods and to actively secrete albumin for longer periods. No such EM deposition was observed when human hepatocytes were cultures with human GBECs. Neither did the co-culture system appear to enhance cell survival or albumin secretion.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended claim 62 to recite a particular ratio of hepatocytes to non-hepatocytes. This limitation has been imported from as-filed claim 69, and claim 69 is now cancelled without prejudice to avoid redundancy. This is neither disclosed nor suggested in the cited references. Table 2.3 of the present application shows an imparted rate of Factor VIII secretion by non-hepatocyte cells when they are co-cultured with hepatocytes. This result taught by present Applicants was not part of the prior art, i.e., the maintenance of the secretory phenotype in the non-hepatocyte/hepatocyte composition, nor could it have been predicted with any reasonable expectation of success.

It is also noted that Clement in the abstract on the first page, states “rat liver epithelial cells could not be replaced by nonhepatic epithelial cells”. This statement teaches away from Applicants’ claims to the use of a set of cells which includes nonhepatic epithelial cells: “gall bladder endothelial cells, bile duct epithelial cells, bile duct endothelial cells, hepatic vessel epithelial cells, hepatic vessel endothelial cells, sinusoid cells and non-parenchymal liver cells.” At page 379 of Clement it was said that hepatocytes and gall bladder epithelial cells did not appear to interact and survival was not increased. These teachings in the cited Clement reference would have discouraged one of ordinary skill in the art from attempting the present claimed invention, and these

teaching would not have provided for any reasonable probability of success in this presently claimed invention.

In view of the foregoing, Applicants respectfully submit that the present claimed invention is not anticipated by the cited Clement reference, nor is the invention as presently claimed *prima facie* obvious over this cited reference. Accordingly, the withdrawal of the rejection is requested.

The Rejections under 35 U.S.C. 103

Claims 62-63, 66-75 and 89 have been rejected under 35 U.S.C. 103(a), as allegedly unpatentable over Clement in view of Kobayashi et al. (2001) Addition Biology, Abstract only. Applicants respectfully traverse this rejection.

Applicants respectfully disagree with the Patent Office position that the invention as claimed is obvious over the cited references. The Patent Office has alleged that the ratio of hepatocytes:nonhepatocytes in claim 69 are considered to be "optimized by routine experimentation". It is said that routine optimization is not patentable even if it results in significant improvements over the prior art, citing In re Aller 105 USPQ 233 (CCPA 1955), unless a new and unexpected result were obtained, for example with the use of critical ranges, and Applicants have the burden of proving criticality.

As discussed above, the cited Clement reference would have been discouraging to one of ordinary skill in the art, in view of the statement that states "rat liver epithelial cells could not be replaced by nonhepatic epithelial cells".

Applicants respectfully maintain that Clement and Kobayashi merely teach an *in vitro* culture system, and neither teaches nor suggests that such cultured cells would be useful as an implantable composition to provide one or more liver metabolic and/or physiologic functions to said recipient comprising non-hepatocyte cells only as claimed in claim 62 or that nonhepatocytes would maintain a secretory phenotype. Neither does

either the cited Clement reference nor the cited Kobayashi abstract teach the use of neonatal non-hepatocytes in their cell compositions. However, the Examiner has taken the position that neonatal material was an obvious selection from the finite number of identified sources of gall bladder epithelial cells. Again it is noted that Clement taught away from the use of gall bladder epithelial cells in a composition comprising hepatocytes and nonhepatocytes. One would not have been motivated to use them in any optimization protocol when other cell types were taught as useful.

Furthermore, neither of the cited references appear to teach or suggest that that non-hepatocytes have the ability to express proteins that are characteristically expressed by hepatocytes so that the claimed compositions could be implanted into a subject with either a disease or a congenital deficiency and have levels of proteins expressed by the implanted cells that would rectify the deficit associated with the disease or deficiency.

Kobayashi appears to describe an *in vitro* system for human gall bladder epithelial cells which did not survive for long periods in cell culture (5 days, with survival for 7 more days but unable to be subcultured). Clement describes a co-culture system of human hepatocytes and RLECs. When Clement replaced the RLEC with human BGECs, the human hepatocytes did not have extended cell survival rate or enhanced albumin secretion. One of ordinary skill in the art, reading Clement, would not be moved to substitute GBEC for the RLEC. In fact, Clement explicitly states that RLEC could not be replaced by non-hepatic epithelial cells (see page 379, column 1, lines 9-11). Clement teaches **away** from the invention.

Kobayashi teaches the co-culture of human gall bladder epithelial cells (GBEC) and human embryo lung fibroblasts (CM-GBF) and who the presence of CM-GF is essential for the growth and differentiation of GBEC in culture.

In view of the foregoing discussion of the references, one of ordinary skill in the art would be motivated to produce a co-culture system of hepatocytes and RLEC, possibly with the addition of CM-GBF to enhance growth and differentiation of hepatocytes in culture. Alternatively, one of ordinary skill in the art might have been likely to try a co-culture system comprising hepatocytes and CM-GBF to see if CM-GBF could replace the positive effect of the RLEC in the method of Clement et al.

Therefore, the two references do not appear to be appropriately combined in the rejection because, from the teachings of the Kobayashi abstract and the Clement reference, one would actually expect a co-culture that was not suitable for implantation for therapy in that there was no extended survival of human hepatocytes *in vitro* and one would not expect extended survival after implantation either. By contrast, the present disclosure provides for a synergistic effect of hepatocytes on the secretion of Factor VIII, an exemplary liver secreted protein, from non-hepatocytes. These unexpected results of present Applicants could not have been predicted from the teachings of the cited references.

Applicants respectfully point out that Clement et al. alone teaches the use of human hepatocytes and rat liver epithelial cells, where **only the hepatocytes** secrete liver secretory factors such as albumin. The RLEC are an essential feature of the *in vitro* co-culture system of Clement to produce the extracellular matrix that appears to protect the hepatocytes and maintain the structure and function in vitro. One of ordinary skill in the art would, not from the teachings of Clement et al. and Kobayashi be motivated to either use RLEC only as a possible implant to provide liver secretory factors to a recipient or to use human GBEC only or a co-culture to provide liver secretory factors to a recipient, for example as part of an implantable composition, as taught and claimed in the present application.

In combination the references still would not have made the present invention obvious because Clement teaches away from the combination of hepatocytes and nonhepatocytes such as gall bladder epithelial cells.

In view of the foregoing discussion, Applicants respectfully maintain that the present claimed invention is not *prima facie* obvious over the cited references, and thus, the reference should be withdrawn.

Conclusion

In view of the foregoing, it is submitted that this case is in condition for allowance, and passage to issuance is respectfully requested.

If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This Amendment is accompanied by a Petition for Extension of Time, Request for Continued Examination and payment of the fees due pursuant to 37 C.F.R. 1.17(a) and 1.17(e). It is believed that this amendment does not necessitate the payment of any additional fees pursuant to 37 C.F.R. 1.16- 1.17. If this incorrect, please charge any further fees due pursuant to the foregoing Rules and grant any extension of time, if necessary, to Deposit Account No. 07-1969.

Respectfully submitted,

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